PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 July 2001 (13.07.01)	
International application No. PCT/EP00/09149	**Applicant's or agent's file reference** 0480/001219
International filing date (day/month/year) 19 September 2000 (19.09.00)	**Priority date** (day/month/year) 24 September 1999 (24.09.99)
Applicant HANTKE, Thomas et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 April 2001 (23.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

KINZEBACH, Werner
Ludwigsplatz 4
67059 Ludwigshafen
ALLEMAGNE

Date of mailing (day/month/year)
13 July 2001 (13.07.01)

Applicant's or agent's file reference
0480/001219

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/09149

International filing date (day/month/year)
19 September 2000 (19.09.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
GOLDSCHEID, Bettina
BASF Aktiengesellschaft
67056 Ludwigshafen
Germany

State of Nationality:
State of Residence:
Telephone No.: 0621/60-78916
Facsimile No.: 0621/60-43123
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
KINZEBACH, Werner
Ludwigsplatz 4
67059 Ludwigshafen
Germany

State of Nationality:
State of Residence:
Telephone No.: 0621/591390
Facsimile No.: 0621/628441
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
A. Karkachi
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TF .TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

KINZEBACH, Werner
Ludwigsplatz 4
67059 Ludwigshafen
ALLEMAGNE

Date of mailing (day/month/year)
11 April 2002 (11.04.02)

Applicant's or agent's file reference
M42109-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/09149

International filing date (day/month/year)
19 September 2000 (19.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
KNOLL AKTIENGESELLSCHAFT
67061 Ludwigshafen
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
ABBOTT GMBH & CO. KG
Max-Planck-Ring 2
D-65205 Wiesbaden
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Lazar Joseph PANAKAL
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TRF^TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

KINZEBACH, Werner
Ludwigsplatz 4
67059 Ludwigshafen
ALLEMAGNE

Date of mailing (day/month/year)
10 April 2002 (10.04.02)

Applicant's or agent's file reference
0480/001219

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/09149

International filing date (day/month/year)
19 September 2000 (19.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
KNOLL AKTIENGESELLSCHAFT
67061 Ludwigshafen
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
ABBOTT Gmbh & Co. KG
Max-Planck-Ring 2
D-65205 Wiesbaden
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Lazar Joseph PANAKAL
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
0480/001219		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/09149	19/09/2000	24/09/1999
International Patent Classification (IPC) or national classification and IPC C07D239/48		
Applicant KNOLL AKTIENGESELLSCHAFT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/04/2001	11.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Beeck, M Telephone No. +49 89 2399 8473

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09149

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-15	as originally filed				

Claims, No.:

1 (part),6-15	as originally filed				
1 (part),2-5	as received on	21/11/2001	with letter of	21/11/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

SECTION V:

1) The documents are numbered according to their sequence in the search report.

2) Document D5 discloses in example 39, column 37, (b) Tablet II, a tablet comprising a 4,6-dianilino-pyrimidine derivative of formula (I), falling under the general formula of present claim 1, and polyvinylpyrrolidone.

Documents D6 and D7 describe substituted 2-anilinopyrimidines, falling under the general formula of present claim 1, with polyvinylpyrrolidone as binding agent (see D6, page 15, line 17, and D7, page 17, line 11).

Document D8 also describes diaminopyrimidine derivatives, falling under the general formula of present claim 1, with polyvinylpyrrolidone as carrier (see page 9, line 21).

P-document D9 has a filing date of 24.3.99, which is before the priority date of the present application, and describes triazine derivatives falling under the general formula of present claim 1, in combination with polyvinylpyrrolidone (see example D1 on page 32).

Also P-document D11 has a filing date before the priority date of the present application. D11 discloses in example D1 on page 30 a formulation of compounds which fall under the general formula of present claim 1 and which contain polyvinylpyrrolidone.

The subject-matter of the claims differs from these documents in that the compounds constitute a **solid solution** in the polymeric matrix.

Therefore the subject-matter of the claims is novel.

It also involves an inventive step, since solid solutions of the compounds are not obvious for the person skilled in the art.

In addition, table 2 of the application shows the high dissolution rate of the

compositions of the invention.

SECTION VI:

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 00 27828	18.5.00	4.11.99	10.11.99

SECTION VII:

The description has not yet been adapted to the wording of new claim 1.

Rec'd on 19 MAR 02

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino or aryl; tetrazole; tetrazole substituted with C_{1-6}alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; oxadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino;

aryl is phenyl or phenyl substituted with C_{1-6}alkyl or halo, and the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom,

as a solid dispersion in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyyrolidone.

2. Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.

3. Particles according to claim 1 or 2, further comprising a surfactant.

4. Particles according to claim 3, wherein the surfactant is a PEG-n-hydrogenated castor oil.

5. Particles according to any of the claims 1 to 3, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
0480/001219		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 09149	19/09/2000	24/09/1999
Applicant		
KNOLL AKTIENGESELLSCHAFT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/09149

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/48 C07D251/18 C07D239/50 C07D403/12 C07D521/00
C07D405/14 A61K31/505 A61P35/00 A61K9/16 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 872 233 A (JANSSEN) 21 October 1998 (1998-10-21) page 1 -page 11 ---	1-5, 10-12, 14,15
Y	EP 0 834 507 A (JANSSEN) 8 April 1998 (1998-04-08) cited in the application page 1 -page 5; claims; tables 2-5 ---	1-5, 10-12, 14,15
Y	WO 99 02523 A (JANSSEN) 21 January 1999 (1999-01-21) cited in the application the whole document --- -/--	1-5, 10-12, 14,15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 2001	31/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/09149

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 13499 A (JANSSEN) 9 May 1996 (1996-05-09) cited in the application page 0; claims; tables 10,11	1-5, 10-12, 14,15
Y	US 5 880 130 A (ANDREW PETER THOMAS) 9 March 1999 (1999-03-09) column 37, line 10 -column 50	1-5, 10-12, 14,15
Y	WO 97 19065 A (CELLTECH) 29 May 1997 (1997-05-29) page 1 -page 15; claims	1-5, 10-12, 14,15
Y	WO 98 41512 A (CELLTECH) 24 September 1998 (1998-09-24) page 1 -page 18; claims	1-5, 10-12, 14,15
Y	WO 91 18887 A (SMITH-KLINE) 12 December 1991 (1991-12-12) page 1 -page 10; claims	1-5, 10-12, 14,15
P,Y	WO 99 50256 A (JANSSEN) 7 October 1999 (1999-10-07) the whole document	1-5, 10-12, 14,15
P,Y	WO 00 27828 A (JANSSEN) 18 May 2000 (2000-05-18) cited in the application page 15; claims	1-5, 10-12, 14,15
P,Y	EP 0 945 443 A (JANSSEN) 29 September 1999 (1999-09-29) the whole document	1-5, 10-12, 14,15

1

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/EP 00/09149

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 872233	A	21-10-1998	NONE		
EP 834507	A	08-04-1998	AU	3926697 A	09-04-1998
			BR	9704937 A	06-06-2000
			CA	2216486 A	01-04-1998
			CN	1180698 A	06-05-1998
			CZ	9702993 A	11-11-1998
			HR	970526 A	31-10-1998
			HU	9701596 A	28-06-1999
			JP	10114759 A	06-05-1998
			NO	974368 A	02-04-1998
			PL	322369 A	14-04-1998
			SG	53075 A	28-09-1998
			SK	131997 A	11-06-1999
			TR	9701070 A	21-04-1998
			TW	411335 B	11-11-2000
			ZA	9708766 A	30-03-1999
WO 9902523	A	21-01-1999	AU	8857598 A	08-02-1999
			AU	8857698 A	08-02-1999
			BG	103934 A	30-11-2000
			BR	9811676 A	19-09-2000
			BR	9811679 A	19-09-2000
			CN	1262675 T	09-08-2000
			CN	1262684 T	09-08-2000
			WO	9902496 A	21-01-1999
			EP	1000029 A	17-05-2000
			EP	1068200 A	17-01-2001
			HR	20000004 A	31-12-2000
			HR	20000007 A	31-12-2000
			HU	0003078 A	29-01-2001
			JP	2000515560 T	21-11-2000
			NO	20000093 A	10-03-2000
			PL	337648 A	28-08-2000
			SK	182999 A	14-08-2000
			SK	184199 A	11-07-2000
			TR	200000020 T	21-09-2000
WO 9613499	A	09-05-1996	AP	779 A	03-11-1999
			AT	198889 T	15-02-2001
			AU	697744 B	15-10-1998
			AU	3868095 A	23-05-1996
			BG	101402 A	31-10-1997
			BR	9509436 A	06-01-1998
			CZ	9701198 A	18-03-1998
			DE	69519995 D	01-03-2001
			EP	0788496 A	13-08-1997
			FI	971784 A	25-04-1997
			HR	950532 A	31-08-1997
			HU	77360 A	30-03-1998
			IL	115771 A	29-02-2000
			JP	3025907 B	27-03-2000
			JP	9511759 T	25-11-1997
			KR	227231 B	01-11-1999
			NO	971895 A	24-04-1997
			NZ	295353 A	26-08-1998
			PL	319905 A	01-09-1997
			RU	2144032 C	10-01-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[illegible] 00/09149

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9613499	A		SK	50797 A	08-04-1998
			TR	960337 A	21-06-1996
			US	5521186 A	28-05-1996
			US	5929075 A	27-07-1999
			ZA	9509084 A	29-04-1997
US 5880130	A	09-03-1999	AU	1194895 A	27-06-1995
			EP	0733045 A	25-09-1996
			WO	9515952 A	15-06-1995
			JP	9506363 T	24-06-1997
			ZA	9409546 A	23-06-1995
WO 9719065	A	29-05-1997	AU	7631496 A	11-06-1997
			EP	0862560 A	09-09-1998
			US	5958935 A	28-09-1999
WO 9841512	A	24-09-1998	AU	6411698 A	12-10-1998
			EP	0970056 A	12-01-2000
			US	6048866 A	11-04-2000
WO 9118887	A	12-12-1991	AU	7971691 A	31-12-1991
WO 9950256	A	07-10-1999	AU	3599799 A	18-10-1999
			BR	9909197 A	05-12-2000
			EP	1066269 A	10-01-2001
			NO	20004809 A	24-11-2000
			TR	200002761 T	22-01-2001
			US	6150360 A	21-11-2000
			EP	0945447 A	29-09-1999
WO 0027828	A	18-05-2000	AU	1046200 A	29-05-2000
			WO	0122938 A	05-04-2001
EP 945443	A	29-09-1999	AU	3599699 A	18-10-1999
			BR	9909191 A	05-12-2000
			WO	9950250 A	07-10-1999
			NO	20004810 A	26-09-2000
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(71) Applicant *(for all designated States except US)*: **KNOLL AKTIENGESELLSCHAFT** [DE/DE]; 67061 Ludwigshafen (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HANTKE, Thomas** [DE/DE]; Landauerstrasse 5, 67067 Ludwigshafen (DE). **REHBOCK, Bettina** [DE/DE]; Wasgauring 28, 67125 Dannstadt (DE). **ROSENBERG, Jörg** [DE/DE]; Bruchstrasse 29, 67158 Ellerstadt (DE). **BREITENBACH, Jörg** [DE/DE]; Hans-Sachs-Ring 95A, 68199 Mannheim (DE).

(74) Agent: **GOLDSCHEID, Bettina**; BASF Aktiengesellschaft, 67056 Ludwigshafen (DE).

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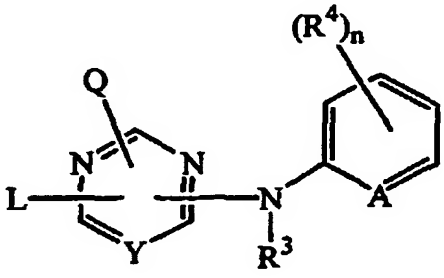
(54) Title: RATE-CONTROLLED PARTICLES



(I)

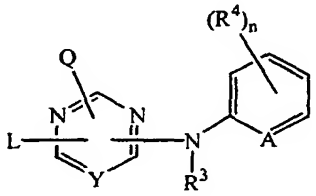
(57) Abstract: Rate-controlled particles, comprising compounds of formula (I) as a solid dispersion.

Rate-controlled particles

Specification

The present invention concerns pharmaceutical compositions in the form of rate-controlled particles, comprising compounds of the formula (I) to (VI)

(I) is an antiviral compound of formula



(I)

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

Y is CR^5 or N;
A is CH, CR^4 or N;
n is 0, 1, 2, 3 or 4;
Q is $-NR^1R^2$ or when Y is CR^5 then Q may also be hydrogen;
R^1 and R^2 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)-amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxy-C_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C_{1-6}alkyl)amino, aryl and Het; or
R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}-alkylidene;
R^3 is hydrogen, aryl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxy-carbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxycarbonyl; and
each R^4 independently is hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalo-methyloxy, or when Y is CR^5 then R^4 may also represent C_{1-6}alkyl substituted with cyano or aminocarbonyl;
R^5 is hydrogen or C_{1-4}alkyl;
L is $-X^1-R^6$ or $-X^2-Alk-R^7$ wherein

R^6 and R^7 each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR^5 then R^6 and R^7 may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then R^6 and R^7 may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;

X^1 and X^2 are each independently $-NR^3-$, $-NH-NH-$, $-N=N-$, $-O-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

Alk is C_{1-4}alkanediyl; or

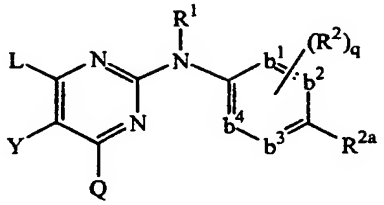
when Y is CR^5 then L may also be selected from C_{1-10}alkyl, C_{3-10}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, or C_{1-10}alkyl substituted with one or two substituents independently selected from C_{3-7}cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, C_{1-6}alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C_{1-6}alkylcarbonyl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro and trifluoromethyl;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

The compounds of formula (I) can be prepared according to the methods described in the patent applications with application number PCT/EP99/02043 and PCT/EP99/02044.

(II) is an antiviral compound of formula



(II)

the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

$-CH=N-C(R^{2a})=CH-CH=$ (b-3);

$-N=CH-C(R^{2a})=N-CH=$ (b-4);

$-N=CH-C(R^{2a})=CH-N=$ (b-5);

$-CH=N-C(R^{2a})=N-CH=$ (b-6);

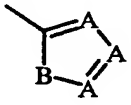
$-N=N-C(R^{2a})=CH-CH=$ (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or $-NR^4R^5$; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$, aryl and Het; or

R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

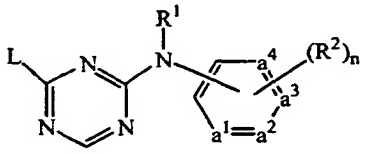
Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^6$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

The compounds of formula (II) can be prepared according to the methods described in the US patent applications with application number 60/143962 and 60/107792.

(III) is an antiviral compound of formula



(III)

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

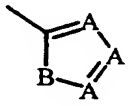
$-CH=CH-CH=CH-$	(a-1);
$-N=CH-CH=CH-$	(a-2);
$-N=CH-N=CH-$	(a-3);
$-N=CH-CH=N-$	(a-4);
$-N=N-CH=CH-$	(a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;

R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl; and

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^4$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino,

polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^4;

B is NH, O, S or NR^4;

p is 1 or 2; and

R^4 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{4-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X-R^3$ wherein

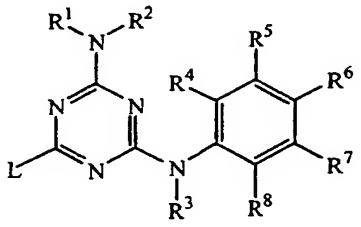
R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy.

The compounds of formula (III) can be prepared according to the methods described in the US patent application with application number 60/107799.

(IV) is an antiviral compound of formula



(IV)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R^1 and R^2 are each independently selected from hydrogen; hydroxy; amino; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; Ar^1; mono- or di(C_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyl)aminocarbonyl; dihydro-2(3*H*)-furanone; C_{1-6}alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyC_{1-6}alkyloxy, carboxyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonyl and thienyl; or

R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-6}alkyl)aminoC_{1-4}alkylidene;

R^3 is hydrogen, Ar^1, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxycarbonyl; and

R^4, R^5, R^6, R^7 and R^8 are each independently selected from hydrogen, hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C_{1-10}alkyl; C_{3-10}alkenyl; C_{3-10}alkynyl; C_{3-7}cycloalkyl; or

L is C_{1-10}alkyl substituted with one or two substituents independently selected from C_{3-7}cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C_{1-6}alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C_{1-6}alkylcarbonyl; and,

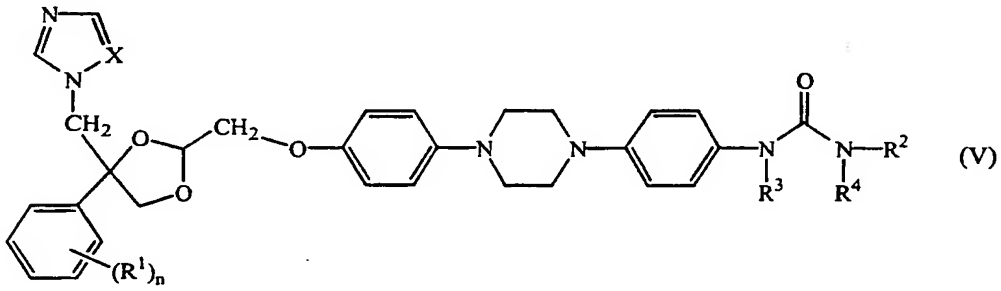
Ar^1 is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R^1/R^2	R^3	R^4	R^5	R^6	R^7	R^8
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH_3	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO_2	H	H
c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C_6H_5	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO_2	H	CH_3	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH_2	H	H
f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF_3	H	H	H
g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	Phenylmethyl	H/H	H	CH_3	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included.

The compounds of formula (IV) can be prepared according to the methods described in EP-A-0834507.

(V) is an antifungal compound of formula



(V)

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

n is zero, 1, 2 or 3;

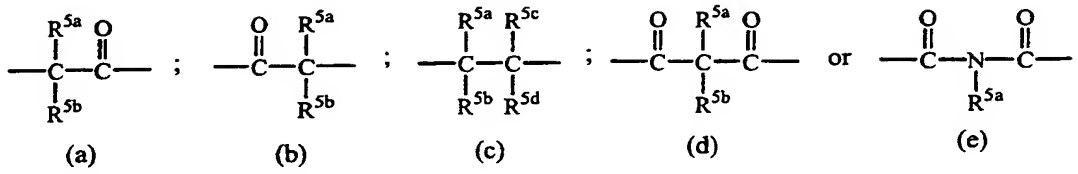
X is N or CH;

each R^1 independently is halo, nitro, cyano, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl;

R^2 is hydrogen; C_{3-7}alkenyl; C_{3-7}alkynyl, aryl; C_{3-7}cycloalkyl; C_{1-6}alkyl or C_{1-6}alkyl substituted with hydroxy, C_{1-4}alkyloxy, C_{3-7}cycloalkyl or aryl;

R^3 and R^4 each independently are hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl; or

R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:



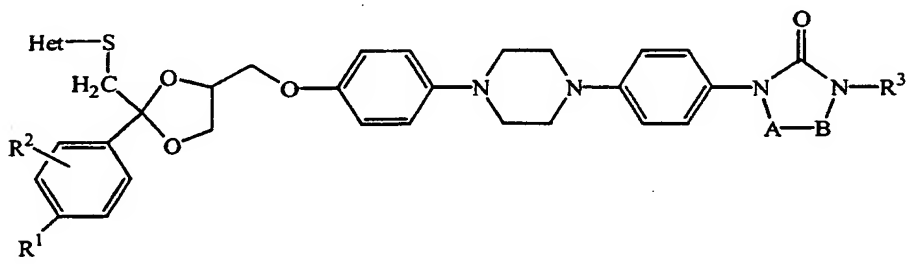
(a) (b) (c) (d) (e)

wherein R^{5a}, R^{5b}, R^{5c}, R^{5d} each independently are hydrogen, C_{1-6}alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl.

The compounds of formula (V) can be prepared according to the methods described in WO 99/02523.

(VI) is an apolipoprotein-B synthesis inhibitor of formula



(VI)

the *N*-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :

$-N=CH-$	(a),
$-CH=N-$	(b),
$-CH_2-CH_2-$	(c),
$-CH=CH-$	(d),
$-C(=O)-CH_2-$	(e),
$-CH_2-C(=O)-$	(f),

in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6}alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6}alkyl;

R^1 is hydrogen, C_{1-6}alkyl or halo;

R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8}alkyl; C_{3-6}cycloalkyl; or C_{1-8}alkyl substituted with hydroxy, oxo, C_{3-6}cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino or aryl; tetrazole; tetrazole substituted with C_{1-6}alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; oxadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino;

aryl is phenyl or phenyl substituted with C_{1-6}alkyl or halo.

The heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom.

The compounds of formula (VI) can be prepared according to the methods described in WO 96/13499.

The particles comprise the compounds of formula (I) to (VI) as a solid dispersion in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone. Furthermore, the invention concerns a process for manufacturing of such particles and pharmaceutical dosage forms comprising such particles.

The compounds of formula (I) to (VI) contained in the particles show poor bio-availability.

In order to improve the dissolution characteristics the compounds are dispersed in a polymeric matrix, preferably by using a melt-extrusion process.

EP-A 0 240 904 discloses a method for producing solid pharmaceutical forms by extrusion of polymer melts which contain active substances, using as polymers homo- or copolymers of N-vinylpyrrolidone.

EP-B 0 580 860 discloses a method for producing solid dispersions of drug substances in a polymeric matrix using a twin screw extruder.

It is an object of the present invention to provide rate-controlled pharmaceutical forms containing the aforementioned compounds.

We have found that this object is achieved by the particles defined at the outset.

Preferred compounds according to the invention are:
4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;
4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-amino]benzonitrile;
4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile;
4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile;
4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile;
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]-amino]benzonitrile;
4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;
1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;

(-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one,
a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

According to the present invention the term "rate-controlled" means that depending on the composition of the matrix the particles can show instant release of the active ingredient or modified release (sustained release).

The compounds according to the invention are homogeneously dispersed in a polymer matrix consisting of a homopolymer of N-vinylpyrrolidone or, preferably, a copolymer of N-vinylpyrrolidone. A preferred copolymer is a copolymer of N-vinylpyrrolidone and vinyl acetate, especially a copolymer obtained from 60% b.w. of NVP and 40% b.w. of vinylacetate.

The polymers show Fikentscher K values of from 17 to 90, preferably a K value of 30 (for the definition of the K value see "H. Fikentscher, Cellulose-Chemie" (1932), 58-64 and 71-74).

The polymeric matrix component is used in amounts of from 40 to 70, preferably of from 50 to 65% b.w. of the total weight of the particles.

In a preferred embodiment of the invention the polymeric matrix further comprises a surfactant, preferably a surfactant with a HLB-value of 10-18 (HLB: Hydrophilic Lipophilic Balance). Especially preferred surfactants are selected form the group consisting of low molecular weight polyoxyethylene polyoxypropylene block copolymers with a mean molecular weight of 1000 to 6000 g/mol, and hydrogenated castor oil which can be modified with polyethylene glycol.

The amounts of surfactants used lies in the range of up to 20% b.w., preferably 5 to 15% b.w., of the particles.

In another preferred embodiment the matrix further comprises an organic carboxylic acid in amounts of up to 5% b.w. of the particles.
In another preferred embodiment of the invention the polymeric matrix further comprises hydroxypropyl methyl cellulose in amounts of up to 25% b.w., preferably from 5 to 10% b.w..

The particles of the present invention are prepared as solid dispersions of the active compounds in a polymeric matrix. The term "solid dispersion" is well known in the art and means a dispersion consisting of solid components. Preferably solid dispersions are in the form of solid solutions wherein the active ingredients are molecularly dispersed in the polymeric matrix.

Such solid dispersion is preferably obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said melt and shaping of the extrudate. The melting is effected by the input of thermal and/or mechanic energy.

Depending on the composition of the matrix, the melting takes place in the range of from 40°C to 190°C, preferably 50 to 150°C. The suitable temperature range depends on the glass transition temperature of the polymer component, the properties of the active ingredients and further additives. The optimal temperature range can be established by a few simple tests.

The mixing of the active substances with the polymer and additional components of the matrix can take place before or after the melting of the polymer. Preferably the process is solvent-free which means that no additional organic solvents or water are added.

The plastification and melting preferably can take place in an extruder, a kneader or a mixing reactor, preferably in an extruder having one or more screws which may rotate in the same direction or opposite directions, especially in a twin screw extruder. The latter can be operated with or without kneading elements, but use of kneading elements is preferred because mixing is better.

The still plastic material is extruded through a die or a breaker plate and then shaped into particles. This may be effected by milling and subsequent sieving the cooled extrudate. The preferred particle size for instant release forms lies in the range of from 0.5 to 1.5 mm.

The particles, optionally together with conventional pharmaceutically acceptable excipients, may be further processed to conventional pharmaceutical dosage forms such as tablets, pastilles, suppositories, or be packed in capsules.

It is possible and particularly advantageous to produce pharmaceutical forms with rate-controlled release and improved dissolution rates of the active ingredients. This was not to be

expected in view of the low solubility of the active ingredients in aqueous media.

Examples

General method

Powder mixes of the components were melt kneaded at 145°C for 5 min.. After cooling the solidified melts were ground and sieved. The sieve fraction 0.5-1.5 mm was used for the dissolution tests.

The composition of the individual powder mixes is listed in Table 1.

Table 1

Example No.	1	2	3	4	5	6
Active ingredient [1)]	30	30	30	30	30	40
VP-VAC-copolymer[2)]	65	55	55	60	55	47,1
Surfactant[3)]	5	15		5	5	4,3
Citric acid				5		
HPMC					10	8,6
Surfactant[4)]			15			

1) 4-[[4-[2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile
2) Kollidon® VA64, VP/VAC = 60/40, BASF Aktiengesellschaft
3) PEG-n-hydrogenated Castoroil
4) polyoxyethylene polyoxypropylene blockcopolymer, mean mol. weight 4000 g/mol

The dissolution tests were carried out according to USP XXIII, paddle model, pH no change test, 0.1 M HCl, at 37°C, 100 rpm

The results are listed in Table 2.

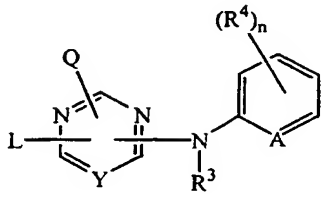
Table 2: Dissolution Rates of particles according to examples 1-6

time [min]	Dissolution [%]				time [min]	Dissolution [%]	
	Ex. 1 (IR)	Ex. 2 (IR)	Ex. 3 (IR)	Ex. 4 (IR)		Ex. 5 (SR)	Ex. 6 (SR)
5	53	65	58	57	1		
10	73	86	88	82	2		
15	77	91	95	89	3		
20	81	91	96	93	4		
30	87	94	99	94	6		
60	92	93	96	94	8	96	95
120	93	94	97	95			
	IR: Instant Release					SR: Sustained Release	

DSC-Measurements were performed with the formulations according to examples 1 to 6 in open pans (air) at temperatures of from 20 → 250°C, with a heating rate of 10°C per minute. There is no indication of crystalline drug substance in the solid dispersions.

Claims

1. Rate-controlled release particles, comprising a compound of formula I



(I)

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

Y is CR^5 or N;

A is CH, CR^4 or N;

n is 0, 1, 2, 3 or 4;

Q is $-NR^1R^2$ or when Y is CR^5 then Q may also be hydrogen;

R^1 and R^2 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)-amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxy-C_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C_{1-6}alkyl)amino, aryl and Het; or

R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}-alkylidene;

R^3 is hydrogen, aryl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyl-oxycarbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxy-carbonyl; and

each R^4 independently is hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyl-oxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR^5 then R^4 may also represent C_{1-6}alkyl substituted with cyano or amino-carbonyl;

R^5 is hydrogen or C_{1-4}alkyl;

L is $-X^1-R^6$ or $-X^2-Alk-R^7$ wherein

R^6 and R^7 each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy,

C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR^5 then R^6 and R^7 may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then R^6 and R^7 may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;

X^1 and X^2 are each independently $-NR^3-$, $-NH-NH-$, $-N=N-$, $-O-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

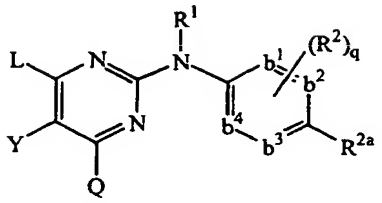
Alk is C_{1-4}alkanediyl; or

when Y is CR^5 then L may also be selected from C_{1-10}alkyl, C_{3-10}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, or C_{1-10}alkyl substituted with one or two substituents independently selected from C_{3-7}cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, C_{1-6}alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C_{1-6}alkylcarbonyl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro and trifluoromethyl;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,

or a compound of formula



(II)

the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

$-CH=N-C(R^{2a})=CH-CH=$ (b-3);

$-N=CH-C(R^{2a})=N-CH=$ (b-4);

$-N=CH-C(R^{2a})=CH-N=$ (b-5);

$-CH=N-C(R^{2a})=N-CH=$ (b-6);

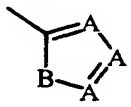
$-N=N-C(R^{2a})=CH-CH=$ (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)amino-carbonyl, C_{1-6}alkyl substituted with cyano, amino-carbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or $-NR^4R^5$; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$, aryl and Het; or

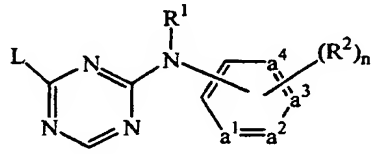
R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^6$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,

or a compound of formula



(III)

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

$-CH=CH-CH=CH-$ (a-1);

$-N=CH-CH=CH-$ (a-2);

$-N=CH-N=CH-$ (a-3);

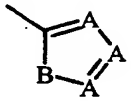
$-N=CH-CH=N-$ (a-4);

$-N=N-CH=CH-$ (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;

R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl; and

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^4$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^4;

B is NH, O, S or NR^4;

p is 1 or 2; and

R^4 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{4-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

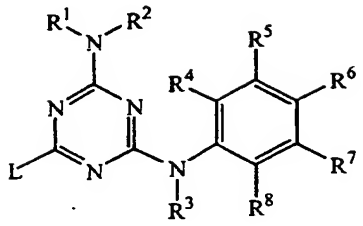
L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy,

or a compound of formula



(IV)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R^1 and R^2 are each independently selected from hydrogen; hydroxy; amino; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; Ar^1; mono- or di(C_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyl)aminocarbonyl; dihydro-2(3*H*)-furanone; C_{1-6}alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyC_{1-6}alkyloxy, carboxyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonyl and thienyl; or

R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-6}alkyl)aminoC_{1-4}alkylidene;

R^3 is hydrogen, Ar^1, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxycarbonyl; and

R^4, R^5, R^6, R^7 and R^8 are each independently selected from hydrogen, hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C_{1-10}alkyl; C_{3-10}alkenyl; C_{3-10}alkynyl; C_{3-7}cycloalkyl; or

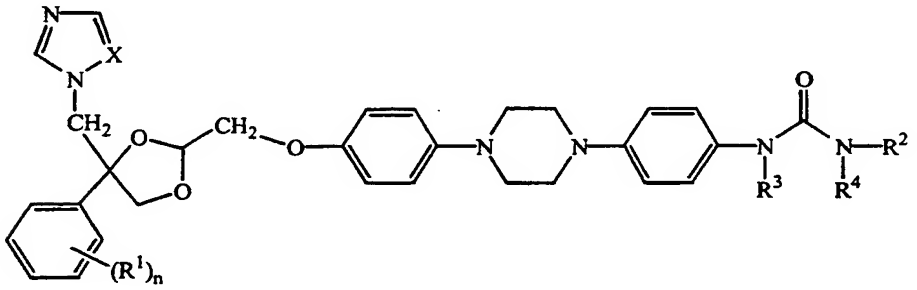
L is C_{1-10}alkyl substituted with one or two substituents independently selected from C_{3-7}cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C_{1-6}alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C_{1-6}alkylcarbonyl; and,

Ar^1 is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R^1/R^2	R^3	R^4	R^5	R^6	R^7	R^8
a	1–(4–(2–methylpropyl)phenyl)ethyl	H/H	H	CH_3	H	H	H	H
b	1–(4–(2–methylpropyl)phenyl)ethyl	H/H	H	H	H	NO_2	H	H
c	1–(4–(2–methylpropyl)phenyl)ethyl	H/H	C_6H_5	H	H	H	H	H
d	1–(4–(2–methylpropyl)phenyl)ethyl	H/H	H	NO_2	H	CH_3	H	H
e	1–(4–(2–methylpropyl)phenyl)ethyl	H/H	H	H	H	NH_2	H	H
f	4–(2–methylpropyl)phenylmethyl	H/H	H	H	CF_3	H	H	H
g	1–(4–(2–methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4–(2–methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4–dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3–dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4–diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2–(3,5–(1,1–dimethylethyl)–4–hydroxy–phenyl)ethyl	H/H	H	H	H	H	H	H
m	2–(3,5–(1,1–dimethylethyl)–4–hydroxy–phenyl)ethyl	H/H	H	H	t–Bu	OH	t–Bu	H
n	Phenylmethyl	H/H	H	CH_3	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included,

or a compound of formula



(V)

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

n is zero, 1, 2 or 3;

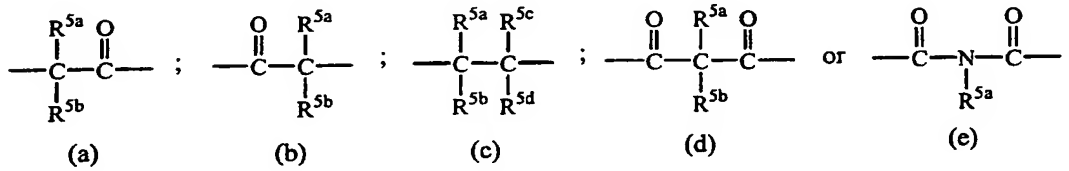
X is N or CH;

each R^1 independently is halo, nitro, cyano, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl;

R^2 is hydrogen; C_{3-7}alkenyl; C_{3-7}alkynyl, aryl; C_{3-7}cycloalkyl; C_{1-6}alkyl or C_{1-6}alkyl substituted with hydroxy, C_{1-4}alkyloxy, C_{3-7}cycloalkyl or aryl;

R^3 and R^4 each independently are hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl; or

R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:

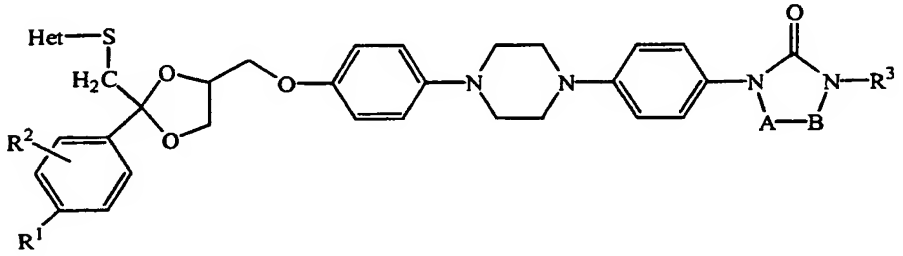


(a) (b) (c) (d) (e)

wherein R^{5a}, R^{5b}, R^{5c}, R^{5d} each independently are hydrogen, C_{1-6}alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl,

or a compound of formula



(VI)

the *N*-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :

$-N=CH-$	(a),
$-CH=N-$	(b),
$-CH_2-CH_2-$	(c),
$-CH=CH-$	(d),
$-C(=O)-CH_2-$	(e),
$-CH_2-C(=O)-$	(f),

in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6}alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6}alkyl;

R^1 is hydrogen, C_{1-6}alkyl or halo;

R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8}alkyl; C_{3-6}cycloalkyl; or C_{1-8}alkyl substituted with hydroxy, oxo, C_{3-6}cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino or aryl; tetrazole; tetrazole substituted with C_{1-6}alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; oxadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino;

aryl is phenyl or phenyl substituted with C_{1-6}alkyl or halo, and the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom,

as a solid dispersion in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyyrolidone.

2. Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.

3. Particles according to claim 1 or 2, further comprising a surfactant.

4. Particles according to claim 3, wherein the surfactant is a PEG-n-hydrogenated castor oil.

5. Particles according to any of the claims 1 to 3, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

6. Particles according to any of the claims 1 to 3, further comprising citric acid in amounts of up to 5 % b.w.

7. Particles according to any of the claims 1 to 6, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70 % b.w. of the total weight of the dosage form.

8. Particles according to claim 7, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 50 to 65 % b.w..

9. Particles according to any of the claims 1 to 8, wherein the controlled release is an instant release of the drug.

10. Particles according to any of the claims 1 to 8, wherein the controlled release is a sustained release.

11. Particles according to claim 10, further comprising hydroxypropyl methyl cellulose in amounts of from 5 to 10 % b.w..

12. Particles according to any of the claims 1 to 11, obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said mixture and shaping of the extrudate.

13. Particles according to any of the claims 1 to 11, comprising a compound selected from the group consisting of
4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile;
4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;
4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-amino]benzonitrile;
4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-
amino]benzonitrile;
4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile;
4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]-amino]benzonitrile;
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;
4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;
1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;
(-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,
a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

14. Pharmaceutical dosage form, comprising particles according to any of the preceding claims.

15. Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

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(71) Applicant *(for all designated States except US)*: **KNOLL AKTIENGESELLSCHAFT** [DE/DE]; 67061 Ludwigshafen (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HANTKE, Thomas** [DE/DE]; Landauerstrasse 5, 67067 Ludwigshafen (DE). **REHBOCK, Bettina** [DE/DE]; Wasgauring 28, 67125 Dannstadt (DE). **ROSENBERG, Jörg** [DE/DE]; Bruchstrasse 29, 67158 Ellerstadt (DE). **BREITENBACH, Jörg** [DE/DE]; Hans-Sachs-Ring 95A, 68199 Mannheim (DE).

(74) Agent: **KINZEBACH, Werner**; Ludwigsplatz 4, 67059 Ludwigshafen (DE).

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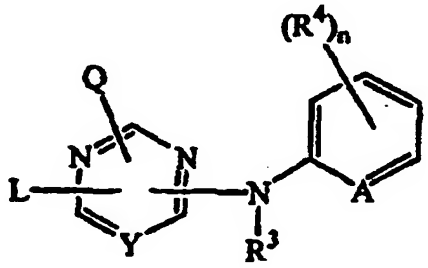
(54) Title: RATE-CONTROLLED PARTICLES



(I)

(57) Abstract: Rate-controlled particles, comprising compounds of formula (I) as a solid dispersion.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/48 C07D251/18 C07D239/50 C07D403/12 C07D521/00
C07D405/14 A61K31/505 A61P35/00 A61K9/16 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Internat[illegible] Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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